Exhibit B

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Trial Design in Migraine Prophylaxis

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In general, the subjective nature of migraine and a high placebo effect generally invalidate open and single-blind trials. Clinical observations, however, most often with drugs used for another indication, e.g. valproate for epilepsy [1], can be hypothesis-generating and should be followed by randomized, controlled clinical trials which are the only way to demonstrate definitely the efficacy of a drug.

Firstly, it should be demonstrated in randomized, double-blind, placebo-controlled, clinical trials that a drug is more effective in migraine prophylaxis than placebo. The drug should then in the optimum dose be compared to currently established treatment for efficacy and tolerability. Whereas there are generally no problems with the comparison with placebo (the drug should be demonstrated to be better than placebo in several studies), the comparison with established drugs often poses problems. Sometimes the new drug is found better than an established drug, but in most trials the two drugs are not found to be statistically significantly different. If the results of these trials are reviewed critically [2, 3], it is often apparent that the trials are too small to demonstrate comparability. Furthermore, if both drugs are found effective by comparison with a baseline period, the improvements noted may be due to the natural history of migraine with amelioration purely with time [4]. Therefore comparative trials should also be placebo-controlled. The numbers of patients needed (see section on statistics) will therefore even in a crossover trial be so big that multi-center trials should be considered. If enough patients cannot be recruited for the trial it is better to avoid doing comparative trials with a low power.

The following is based mainly on the recommendations of the Drug Trial Committee of the International Headache Society (IHS) [5].

Selection of Patients

Migraine Definition. The operational diagnostic criteria of the IHS [6] should be strictly adhered to. In clinical practice there are patients who do not conform to the IHS criteria but, nevertheless, are diagnosed as having migraine, treated accordingly and respond appropriately to prophylactic migraine drugs. For clinical drug trials, however, requirements should be more rigid than in clinical practice. Relatively few people will be excluded by requiring IHS criteria.

Frequency of Attacks. Attacks of migraine should occur 2 to 6 times per month. The frequency of interval headaches should be no more than 6 days per month. There should be at least 24 h of freedom from headache between attacks. A minimum of 2 attacks per month is needed in order to detect a prophylactic effect within a reasonable time, and this is also generally the limit for when to use prophylactic treatment of migraine in clinical practice. An upper limit of migraine attacks is needed in order to avoid inclusion of patients with very frequent attacks because these patients often have drug abuse [7]. Interval headaches of more than 6 per month would begin to blend into attacks of migraine without aura if migraine were to occur as often as 6 per month. Twenty-four hours freedom between attacks of migraine permits identification of individual attacks.

Duration Since Onset. Migraine should have been present for more than one year. A minimum course of one year is advisable to help exclude headaches due to organic disease that may mimic migraine, and to establish a stereotyped pattern for the patient's headaches.

Trial Design

Blinding. Randomized controlled trials in migraine prophylaxis should be double-blind.

Placebo-control. Drugs used for migraine prophylaxis should be compared with placebo. When two presumably active drugs are compared, placebo control should also be included in order to test the reactivity of the patient sample.

The placebo effect in migraine prophylaxis is usually in the range of 20–40% and in some trials even higher, e.g. [8], and a drug should therefore be demonstrated to be superior to placebo. That two presumably active drugs are found equally effective in a trial is no proof of efficacy or comparability. To refer to the previous efficacy of the established drug in other trials is not enough; it is using historical controls, a method largely discouraged in medicine. Both drugs should also be shown to be superior to placebo.

Crossover/Parallel Group Comparison. Both crossover and the parallel group comparison (non-crossover) designs can be used in certain situations. The advantage of the crossover design is that it is approximately eight times more powerful than the non-crossover design in prophylactic migraine trials [9]. For certain non-crossover designs, however, the number of patients required is no more than 2 to 4 times the number required in a crossover design [10]; for further discussion see [11]. The drawbacks of the crossover design is the possibility of a carryover effect; the need for a long total period of treatment (extended by washout periods) that may cause problems with dropouts; and side effects can more easily affect blinding with this design. A period effect is not a problem in the crossover design, because suitable statistical techniques can deal with it [4].

When a drug is compared with placebo or an inferior drug both designs can be used if a carryover effect is not present. If there are indications from previous trials of a carryover effect, the non-crossover design should be used.

In the comparison of two drugs and placebo, the 3-way crossover design should be used. This design, if properly performed, is not invalidated by a possible carryover effect and will result in narrow confidence intervals.

Baseline Recording. A one-month baseline should be used. During baseline, placebo can be given to exclude placebo responders. This will, however, in some cases hinder actual observation of the placebo response later in the trial. The use of placebo during baseline is optional.

Duration of Treatment Periods. Treatment periods of at least 3 months should be used. Relatively long treatment periods are important for the power of the trial and also because the efficacy of many drugs accrues gradually (i.e needs some weeks before becoming fully established). Furthermore, only effects of sufficient duration are clinically relevant. With some drugs with long equilibration half lives [12] longer treatment periods of 4–5 months may be necessary to demonstrate the potential efficacy.

Washout Periods. In crossover trials a washout period of one month should be used. In the crossover design, the effect of treatment in one period must not affect the results in the subsequent period. Since drug effects are often slow in onset and wane gradually, a drug-free (placebo) washout period must be interposed between the trial periods. Its length must exceed the time taken to eliminate both the drug and its effect, which is often unknown. A washout period of one month is recommended as a practically feasible compromise.

Dosage. In assessing any new drug in migraine prophylaxis no assumptions should be made regarding dosage, and attempts should be made to test as wide a range as possible in different trials. As long as the pharmacological background for the efficacy of certain drugs in migraine remains unknown, the choice of doses in trials is a purely empirical compromise between efficacy

and side effects. The willingness of the patients to take the drug for months depends heavily on the ratio between efficacy and side effects. The choice of dose is therefore one of the crucial factors in determining the chances for a successful completion of the trial. This compromise tends to induce the use of sub-optimal doses in prophylactic migraine trials.

Dosage can in triple-blind RCTs be adjusted to a certain plasma level of the drug, e.g. to anti-epileptic plasma concentrations with sodium valproate [13].

So far, no dose-response curve has been established for any drug used in migraine prophylaxis.

Evaluation of Results

Headache Diary. The evaluation of efficacy should be based on a headache diary, which should be consistent with what were identified as the assessment parameters, and should include no more.

Frequency of Attacks. Frequency of attacks per 4 weeks should be the main efficacy parameter. The number of migraine attacks should be recorded irrespective of their duration.

Most trials permit the inclusion of patients with interval headaches, but only if they are able to differentiate them well from migraine attacks. The headache diary should differentiate between the two types of headache by simply asking the patient: 'Is this a true migraine attack or another headache?' When identified, interval headaches may simply be recorded by the number of days per 4 weeks with interval headache.

Number of Days with Migraine. Number of days with migraine per 4 weeks can be used as an assessment parameter. This parameter, which allows the use of a more simple headache diary, where the patient for each day can indicate whether or not a migraine headache was present. In the same diary the patients can also indicate interval headaches, which possibly are migraine fragments.[1]

Severity of Headache. The severity of headache should be noted by the patient on a verbal scale: 0: no headache; 1: mild headache; 2: moderate headache; 3: severe headache. Alternatively, visual analogue scales can be used. One should be aware that patients are probably rating the maximum headache of the attack. Furthermore, acute treatment may possibly modify severity,

[1] In the earlier phases evaluation of a drug for migraine prophylaxis frequency of attacks should be preferred as the primary efficacy parameter, since number of days with migraine mixes up the frequency and duration of attacks, the latter being also dependent on acute treatment of attacks.

independently of the trial drug. Severity of headache should thus probably not be used as a primary efficacy parameter.

Duration in Hours. Patients should be asked to record time of start and time of end of attacks (in their view only), as raw data. Measurement of duration is difficult because of uncertainties relating to time of onset, time of offset and interaction of sleep. Duration of attacks should therefore not be chosen as a primary efficacy parameter.

Headache Index. The use of headache indices is not recommended. Conceivably the headache indices (I: frequency × severity and II: frequency × severity × duration) reflect the total suffering of the patients. There are, however, considerable problems with both severity and duration and when used in the headache indices, faulty weighting in the arbitrary numerical severity score will be increased by multiplication. Most important, the headache indices can in no meaningful way be compared among subjects, and a certain decrease in a headache index is difficult to evaluate clinically. Lastly, there is no need for headache indices, because in most cases where a decrease is found this is due to a decrease in frequency of attacks [14].

Patients' Preferences. The use of patients' preferences is not recommended. Patients' preferences for one or other treatment can be asked only in a crossover trial and is not recommended because it can endanger the blinding of patients since the design of the study has to be disclosed.

Responders (50% Effect). The number of responders can be expressed as those with a more than 50% reduction in attack frequency during treatment compared with the baseline period. The choice of more than 50% reduction is traditional and arbitrary. This parameter is insensitive, but can probably be used as a way of identifying retrospectively subgroups of responders. Number of responders can be used in meta-analysis of placebo-controlled RCTs with the same drug. Alternatively, time series analysis [15] can be used in defining responders.

Side Effects. All adverse events, not necessarily the same as side effects, occurring in the treatment periods should be recorded. Side effects are especially important in prophylactic trials since in clinical practice many patients stop such treatment because of them. So if the report of such a trial indicates that active drug and placebo give rise to similar side effect incidences the result should be treated with caution, as it is probably due either to the trial including too few patients or to an inadequate adverse events reporting system.

Statistics

Calculations of sample sizes in prophylactic crossover and non-crossover trials, based on frequency of attacks, indicate that the former has eight times

more power than the latter for detecting a certain effect [9]. For practical purposes one can detect a difference with both designs. If, however, comparability between two drugs is to be demonstrated, only the crossover design will be suitable. In this case, as mentioned above, placebo should also be included, and this 3-way crossover design, if properly conducted, is not invalidated by a possible carryover effect (Tfelt-Hansen, pers. observ.).

In the non-crossover design, comparisons between groups can be made either as comparisons during the treatment periods or as comparisons of changes from baseline. The latter is conceivably more powerful, but analyses have so far only shown a marginal increase in power (Tfelt-Hansen, pers. observ.). In non-crossover trials the use of the baseline value as a covariate should also be examined.

References

1 Sørensen KV. Valproate: A new drug in migraine prophylaxis. Acta Neurol Scand 1988;78:346–348.
2 Tfelt-Hansen P: Efficacy of beta-blockers in migraine. A critical review. Cephalalgia 1986;6(suppl 5): 15–24.
3 Olesen J: The role of calcium entry blockers in the prophylaxis of migraine. Eur Neurol 1986; 25(suppl 1):72–79.
4 Olesen J, Krabbe AÆ, Tfelt-Hansen P: Methodological aspects of prophylactic drug trials in migraine. Cephalalgia 1981;1:127–141.
5 International Headache Society Committee on Clinical Trials in Migraine: Guidelines for controlled trials of drugs in migraine, ed 1. Cephalalgia 1991;11:1–12.
6 Headache Classification Committee of the International Headache Society: Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8(suppl 7): 1–96.
7 Diener H-C, Tfelt-Hansen P: Headache associated with chronic use of substances; in Olesen J, Tfelt-Hansen P, Welch KMA (eds): The Headaches, ed 1. New York, Raven Press, 1993, pp 721–727.
8 Migraine-Nimodipine European Study Group (MINES): European multicenter trial of nimodipine in the prophylaxis of classic migraine (migraine with aura). Headache 1989;29:639–642.
9 Tfelt-Hansen P, Nielsen SL: Patients numbers needed in prophylactic migraine trials. Neuroepidemiology 1987;6:214–219.
10 Lewis JA: Migraine trials: Crossover or parallel group. Neuroepidemiology 1987;6:198–208.
11 Olesen J, Tfelt-Hansen P: Headache; in Porter RJ, Schoenberg BS (eds): Controlled clinical trials in neurological disease. Boston, Dortrecht, London, Kluwer Academic Publishers, 1990, pp 185–201.
12 Sørensen P, Hansen K, Olesen J: A placebo-controlled, double-blind, crossover trial of flunarizine in common migraine. Cephalalgia 1986;6:7–14.
13 Jensen R, Brinck T, Olesen J: Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study. Neurology 1994;44:647–651.
14 Tfelt-Hansen P, Standnes B, Kangasneimi P, Hakkarainen H, Olesen J: Timolol vs propranolol vs placebo in common migraine prophylaxis. Acta Neurol Scand 1984;69:1–8.
15 Langohr HD, Gerber WD, Koletzki E, Mayer K, Schroth G: Clomipramine and metoprolol in migraine prophylaxis – a double-blind crossover study. Headache 1985;25:107–113.

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